

We claim:

1. A modified therapeutic peptide capable of forming a peptidase stabilized therapeutic peptide composed of between 3 and 50 amino acids, said peptide having a carboxy terminal amino acid, an amino terminal amino acid, a therapeutically active region of amino acids and a less therapeutically active region of amino acids, said peptide comprising:
  - a reactive group which reacts with amino groups, hydroxyl groups, or thiol groups on blood components to form a stable covalent bond thereby forming the peptidase stabilized therapeutic peptide wherein the reactive group is selected from the group consisting of succinimidyl and maleimido groups and wherein the reactive group is attached to an amino acid positioned in said less therapeutically active region of amino acids.
2. The peptide of claim 1 wherein said therapeutically active region of amino acids includes said carboxy terminal amino acid and said reactive group is attached to said amino terminal amino acid.
3. The peptide of claim 1 wherein said therapeutically active region of amino acids includes said amino terminal amino acid and said reactive group is attached to said carboxy terminal amino acid.
4. The peptide of claim 1 wherein said therapeutically active region of amino acids includes said carboxy terminal amino acid and said reactive group is attached to an amino acid positioned between said amino terminal amino acid and said carboxy terminal amino acid.
5. The peptide of claim 1 wherein said therapeutically active region of amino acids includes said amino terminal amino acid and said

reactive group is attached to an amino acid positioned between said amino terminal amino acid and said carboxy terminal amino acid.

6. A method of synthesizing the modified therapeutic peptide of  
5 claim 1, comprising:

- if said therapeutic peptide does not contain a cysteine, then synthesizing said peptide from said carboxy terminal amino acid and adding said reactive group to said carboxy terminal amino acid, or adding a terminal lysine to said carboxy terminal amino acid and adding  
10 said reactive group to said terminal lysine;
- if said therapeutic peptide contains only one cysteine, then reacting said cysteine with a protective group prior to addition of said reactive group to an amino acid in said less therapeutically active region of said peptide;
- 15 if said therapeutic peptide contains two cysteines as a disulfide bridge, then oxidizing said two cysteines and adding said reactive group to said amino terminal amino acid, or to said carboxy terminal amino acid, or to an amino acid positioned between said carboxy terminal amino acid and said amino terminal amino acid of said therapeutic  
20 peptide; and
- 25 if said therapeutic peptide contains more than two cysteines as disulfide bridges, then sequentially oxidizing said cysteines in said disulfide bridges and purifying said peptide prior to the addition of said reactive groups to said carboxy terminal amino acid.

7. A method for protecting a therapeutic peptide from peptidase activity in vivo, said peptide being composed of between 3 and 50 amino acids and having a carboxy terminus and an amino terminus and a carboxy terminal amino acid amino acid and an amino terminal amino  
30 acid, comprising:  
(a) modifying said peptide by attaching a reactive group to the carboxy terminal amino acid, to the amino terminal amino acid, or to an

Cont

A1

amino acid located between the amino terminal amino acid and the carboxy terminal amino acid, such that said modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component;

5        (b)      forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity; and

          (c)      analyzing the stability of said peptide-blood component

10      conjugate to assess the protection of said peptide from peptidase activity.

RULE  
126

8.      A method according to claim 7, further comprising the step of administering said modified peptide in vivo before step (b), such that the

15      peptide-blood component conjugate is formed in vivo.

9.      A method according to claim 7, wherein step (b) occurs ex vivo.

10.     A method according to claim 7 wherein step (c) is performed in

20      vivo.

A2  
scr

11.     A method according to claim 7, wherein said reactive group is a maleimido group.

25

12.     A method according to claim 7, wherein said reactive group is attached to said peptide via a linking group.

30      13.     A method according to claim 7, wherein said blood component is albumin.

14. A method according to claim 7, wherein one or more of said amino acids is synthetic.

15. A method for protecting a therapeutic peptide from peptidase activity in vivo, said peptide being composed of between 3 and 50 amino acids and having a therapeutically active region of amino acids and a less therapeutically active region of amino acids, comprising:

- determining said therapeutically active region of amino acids;
- modifying said peptide at an amino acid included in said less therapeutically active region of amino acids by attaching a reactive group to said amino acid to form a modified peptide, such that said modified peptide has therapeutic activity and is capable of forming a covalent bond in vivo with a reactive functionality on a blood component;
- forming a covalent bond between said reactive entity and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity; and
- analyzing the stability of said peptide-blood component conjugate to assess the protection of said peptide from peptidase activity.

16. A method according to claim 16, further comprising the step of administering said modified peptide in vivo before step (c), such that the peptide-blood component conjugate is formed in vivo.

17. A method according to claim 18, wherein step (c) occurs ex vivo.

18. A method according to claim 19, wherein step (d) is performed in vivo.

18 20. A method according to claim 18, wherein step (c) is performed in vivo.

20 21. A method according to claim 20, wherein step (d) is performed ex vivo.

~~Sub Ay~~ 21. 15 A method according to claim 16, wherein said peptide has a carboxy terminus, an amino terminus, a carboxy terminal amino acid and an amino terminal amino acid, and wherein step (b) further comprises:

10 (a) if said less therapeutically active portion is located at the carboxy terminus of said peptide, then modifying said peptide at the carboxy terminal amino acid of said peptide;

(b) if said less active portion is located at the amino terminus of said peptide, then modifying said peptide at the amino terminal amino acid of said peptide; and

15 (c) if said less active portion is located at neither the amino terminus nor the carboxy terminus of said peptide, then modifying said peptide at an amino acid located between the carboxy terminus and the amino terminus.

20 22. 15 A method according to claim 16, wherein said reactive group is a maleimido group.

23 24. 15 A method according to claim 16, wherein said reactive entity is attached to said peptide via a linking group.

24 25. 15 A method according to claim 16, wherein said blood component is albumin.

30 25 26. 15 A method according to claim 16, wherein one or more of said amino acids is synthetic.